

Hepatitis Update 2004

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Outline

Approach to Abnormal Liver Enzymes

Fatty Liver Disease

Viral hepatitis

Genetic Liver Disease

Board potpourri

ALT and AST

Have been in use since 1955

**Normal Range: “Healthy Population”
± 2 S.D.**

ALT levels are influenced by:

Gender

Weight

Lipids

Glucose intolerance

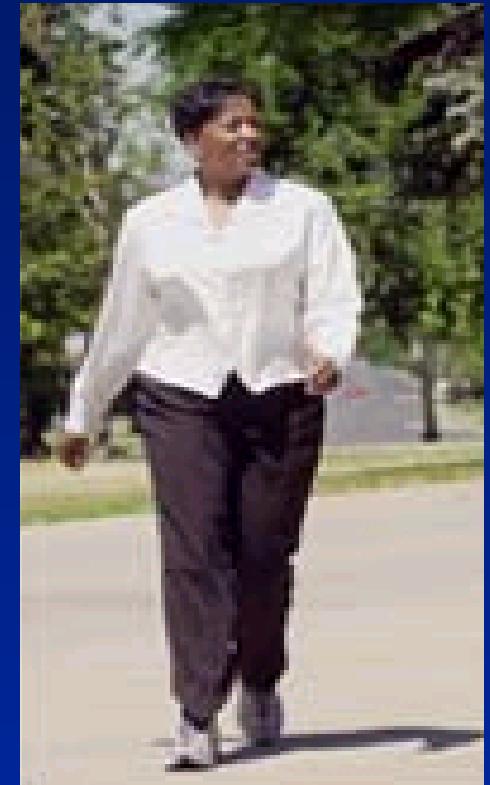
Prati et al. *Environ Health Perspect* 2002;110:117-124

Calculating the ALT (U/L) normal

Healthy Blood Donors	Median	5 th	25 th	75 th	95 th	95 th	Historical
N=6835	12	6	9	17	32		
Male 40	15	8	11	21	36		
Female 30	9	6	8	13	21		
BMI < 25							
N=3927	11	6	9	15	26		
Male 40	13	8	10	18	30		
Female	9	6	8	12	19		

What do I really not want to miss?

- ♦ **Potentially treatable liver diseases**
 - Autoimmune hepatitis
 - Hemochromatosis
 - Medications and ETOH
 - Malignancy
 - Hepatitis B and C
 - Biliary obstruction
 - Wilson's Disease



Evaluation Abnl ALT - AST

- ◆ **Hepatitis B and C Serology**
- ◆ **ANA** (autoimmune hepatitis)
- ◆ **ASMA** (autoimmune hepatitis)
- ◆ **A1AT** (alpha 1- antitrypsin deficiency)
- ◆ **Ferritin & iron panel** (hemochromatosis)
- ◆ **Ceruloplasmin** (Wilson's disease)
- ◆ **Lipid Panel, glucose, HbA1C** (fatty liver)
- ◆ **Ultrasound**

Significance of LAE Elevation Marker Negative Workup

N = 81 6 mos persistently elevated LAE

51% - Steatosis (Fatty Liver)

32% - Steatohepatitis (Fatty liver w/
inflammation)

10% - Normal

5% - Fibrosis

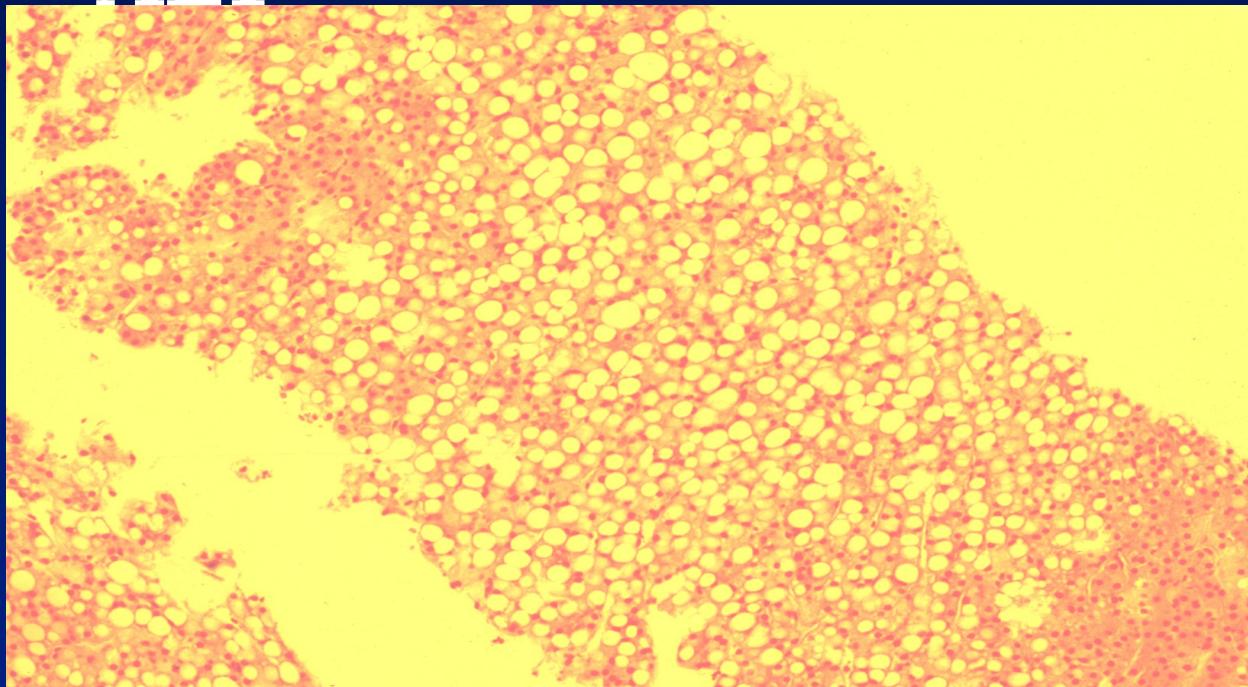
2% - Cirrhosis



Fatty Liver

ALT

70-80% Asym.



Risks:

- Obesity
- Diabetes
- Alcohol
- Hyperlipidemia
- Medications
7-12% fibrosis and inflammation

Normal

Nonalcoholic Fatty Liver Disease

“N

Steatosis

Prognosis - Excellent

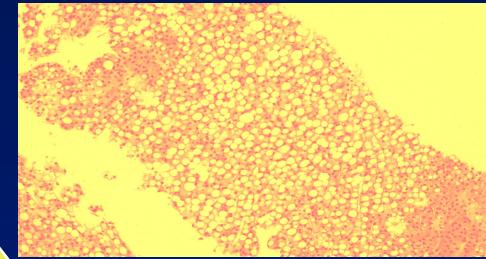
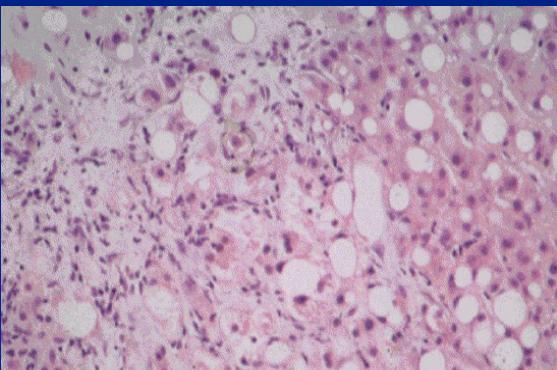
NASH

Prognosis - ?

20% cirrhosis

Steatosis with
mild
inflammation

Prognosis - Good





What is the threshold at which steatohepatitis becomes ETOH related?



High 14-28 units a week

Medium 14 units a week

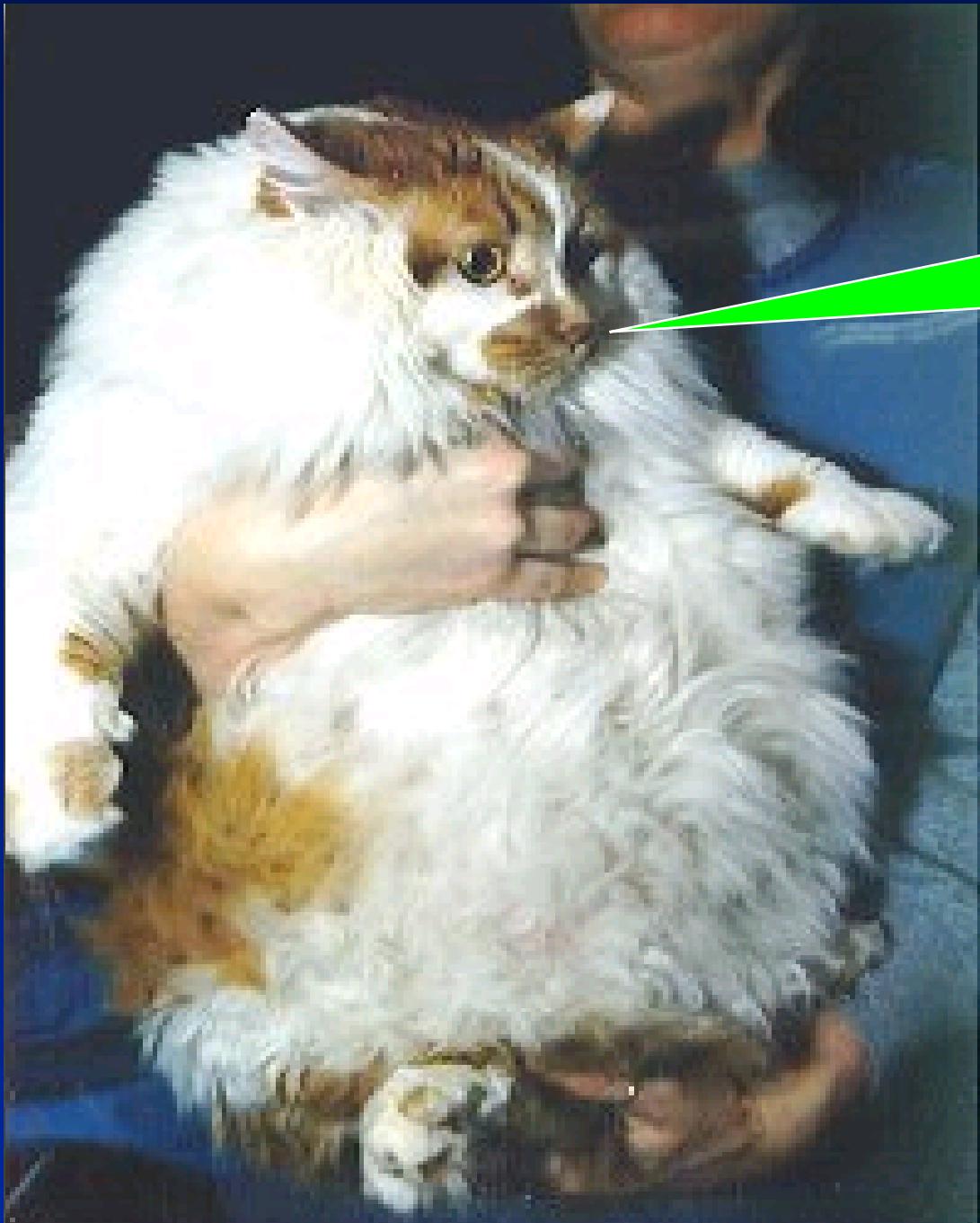
Low 7 units a week

Men 2-4 units/day

Women 2

WRAMC NASH Study

- ♦ N = 16 patients (1996)
- ♦ Over 5 year period 3 patients found ETOH +
 - Consult from alcohol rehab unit
 - DUI
 - Admitted heavy alcohol intake on a f/u visit
- ♦ 18.75% of initial cohort was + for ETOH



I swear I
don't drink!

Epidemiology of fatty liver



Prevalence of NASH in Autopsy Series



Obese

Steatosis

70%

NASH

35%

Lean

35%

2.7%

Differential of NASH in NL BMI Pt.

- ◆ Drug toxicity
- ◆ Lipid disorder
- ◆ Familial Metabolic disorder
- ◆ Central obesity
- ◆ Occult insulin resistance
- ◆ ETOH

NASH: Not Just An Adult Disease



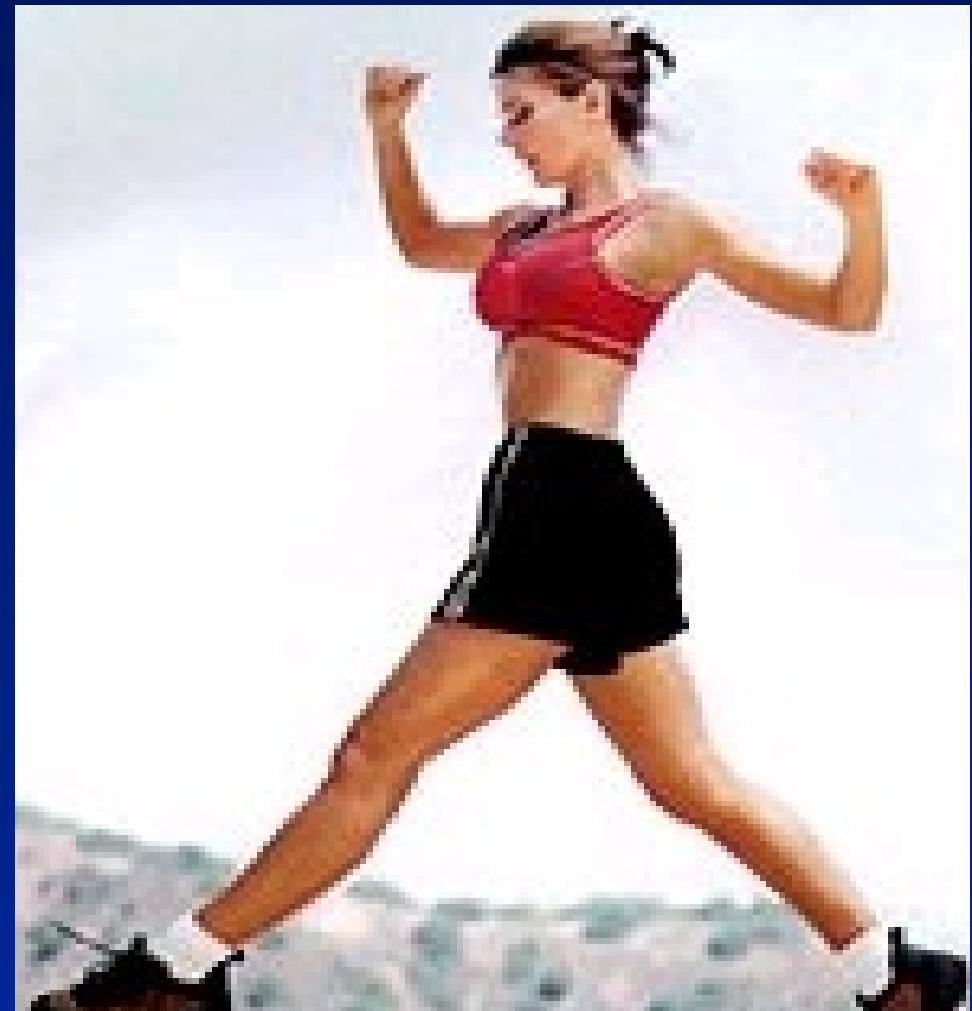
NASH - Most common liver disease of Adolescents

Biopsy?

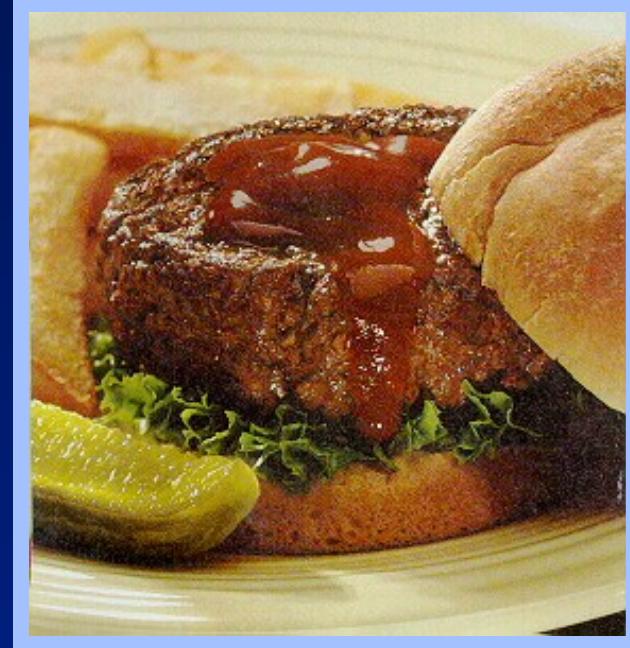
- ◆ Clinical judgement
 - Not comfortable with diagnosis?
 - Staging important?
- ◆ Consider after 6-12 months trial of wt loss
- ◆ Cost and risk mitigate against biopsy with exceptions above stated

Treatment

- ◆ Vitamin E
- ◆ Vitamin C
- ◆ Ursodiol
- ◆ Betaine
- ◆ S-adenosylmethionine (SAM)
- ◆ Metformin
- ◆ Glitazone
- ◆ Gemfibrozil
- ◆ Statins
- ◆ Orlistat
- ◆ Weight Loss and exercise



Hepatitis A: Transmission



Velma

Updated: 09:49 PM EST

Hepatitis Outbreak Linked to Green Onions

Three Killed, Nearly 600 Sickened

By JOE MANDAK, AP



BEAVER, Pa. (Nov. 21) -- A hepatitis A outbreak that has killed three people and sickened nearly 600 others who ate at a Chi-Chi's Mexican restaurant was probably caused by green onions from Mexico, health officials said Friday. But how the scallions became tainted remains unclear.

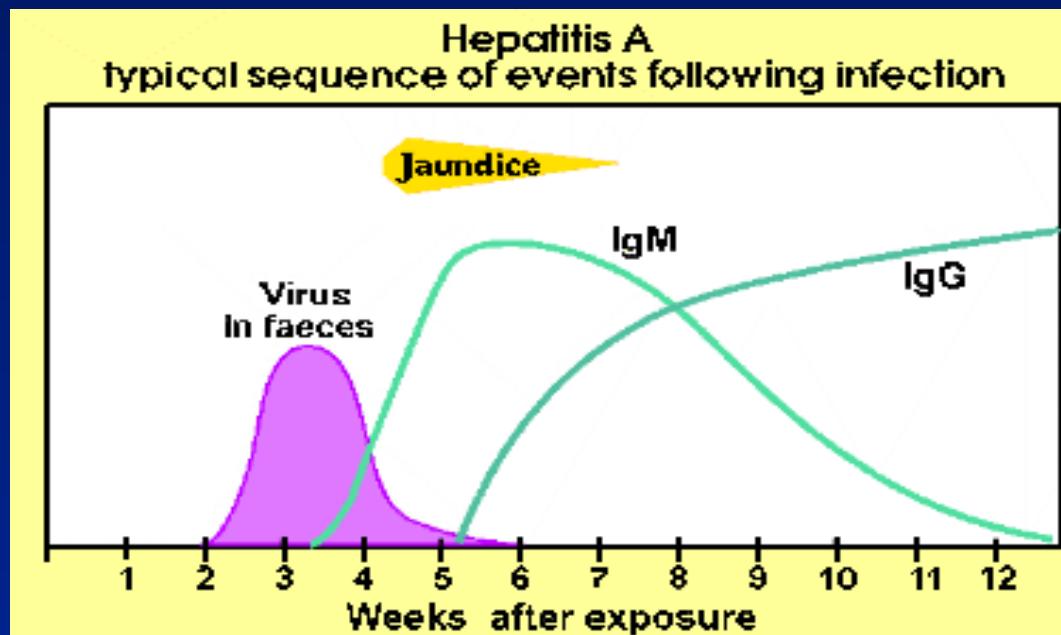
All the hepatitis A cases at the restaurant 25 miles northwest of

**She's as
excited as
you are.**



Diagnosis

- ◆ Serum HAV-IgM is the test of choice for acute infection.
- ◆ IgG is reserved for to determine immune status.
(Total HAV)



Hepatitis B

- Percutaneous and Perinatal transmission
- Incubation - 60 days
- Chronic Hepatitis - Younger the age of infection, the higher the risk for chronicity
- Vaccine is available
- Post-exposure tx - HBIG
- 350 million carriers world wide, increases chance for liver cancer by 100 fold.

Spectrum of Hepatitis B

- ◆ Acute, self-limited hepatitis
- ◆ Fulminate hepatitis
- ◆ Chronic Carrier State
 - Non replicator
 - Ongoing viral replication



Hepatom
a

Cirrhosis

Hepatitis B Serology

- Anti-HBS antibodies
- Anti-HBc IgM
- Anti-HBc IgG
- Anti-HBe
- ◆ HBsAg antigen
- ◆ HBeAg
- ◆ HBV DNA
- ❖ Delta IgM
- ❖ Delta antigen

Delta hepatitis

Hepatitis B Treatment

- Acute HBV: Supportive
- Chronic HBV (Replicators): can be treated with Interferon alfa, lamivudine or adefovir
- Chronic HBV Carrier (non-replicator): Follow with AFP and Liver ultrasound to monitor for HCC

Isolated Hepatitis B core Antibody

- Acute HBV: isolated anti-HBc IgM
Window period between clearing of HBsAg and onset of development of anti-HBs.

Anti-HBc IgG

Cleared virus – inadequate anti-HBs production

False positive

Proceed with vaccination

MIDEAST HOW A NEW PEACE PLAN MIGHT WORK

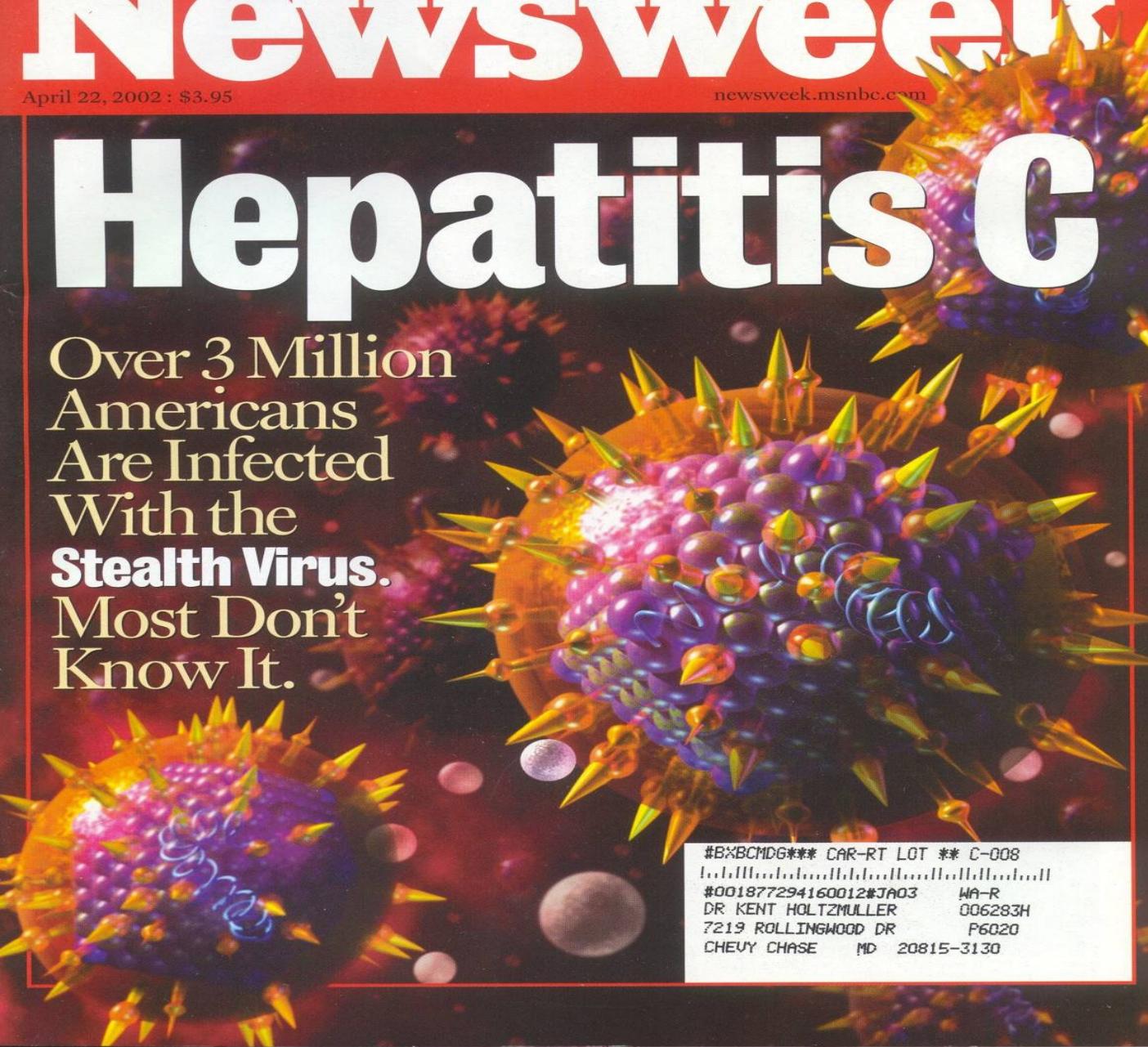
Newsweek

April 22, 2002 : \$3.95

newsweek.msnbc.com

Hepatitis C

Over 3 Million
Americans
Are Infected
With the
Stealth Virus.
Most Don't
Know It.



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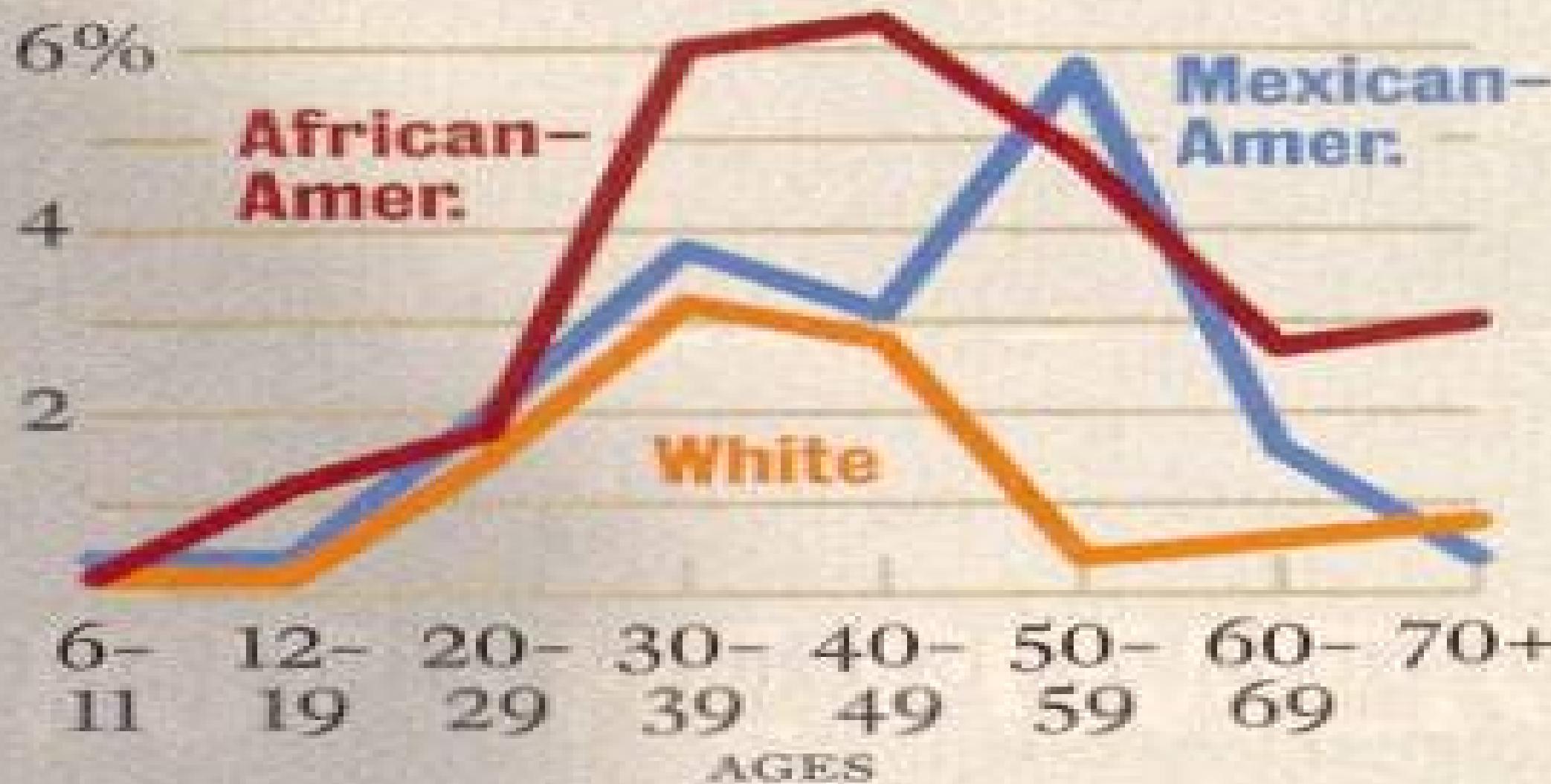
Most common
cause for:

Liver Transplant
HCC (in U.S.)

Major cause of
mortality in HIV

HCV

By age and race, 1988–1994



Projected mortality HCV

19

16

13

2002

2010

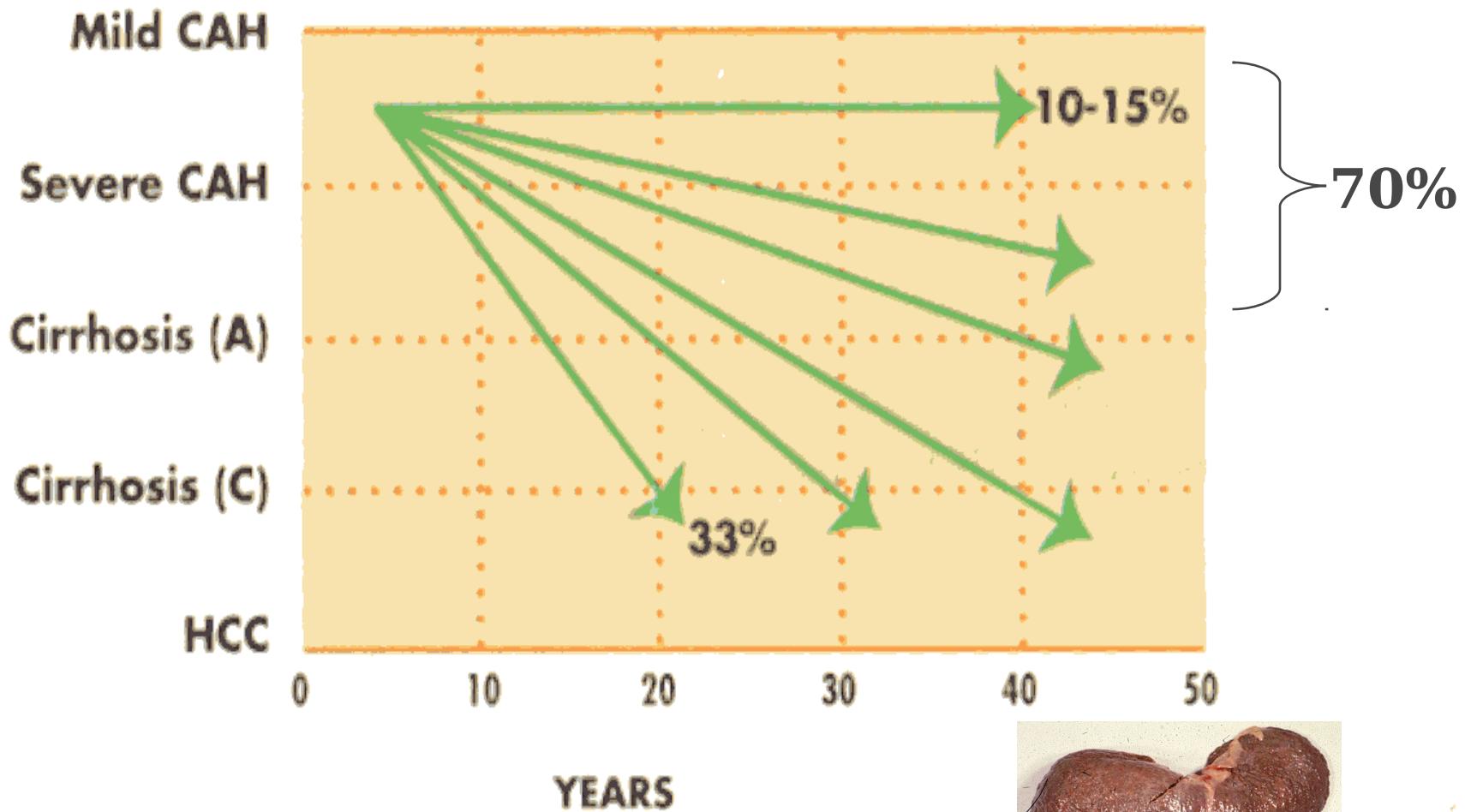
2020

Hepatitis C deaths

IN THOUSANDS

RESEARCH AND TEXT BY JOSH JULICK,
GRAPHIC BY CHRISTOPH BLUMRICH—NEWSWEEK

NATURAL HISTORY OF CHRONIC HCV

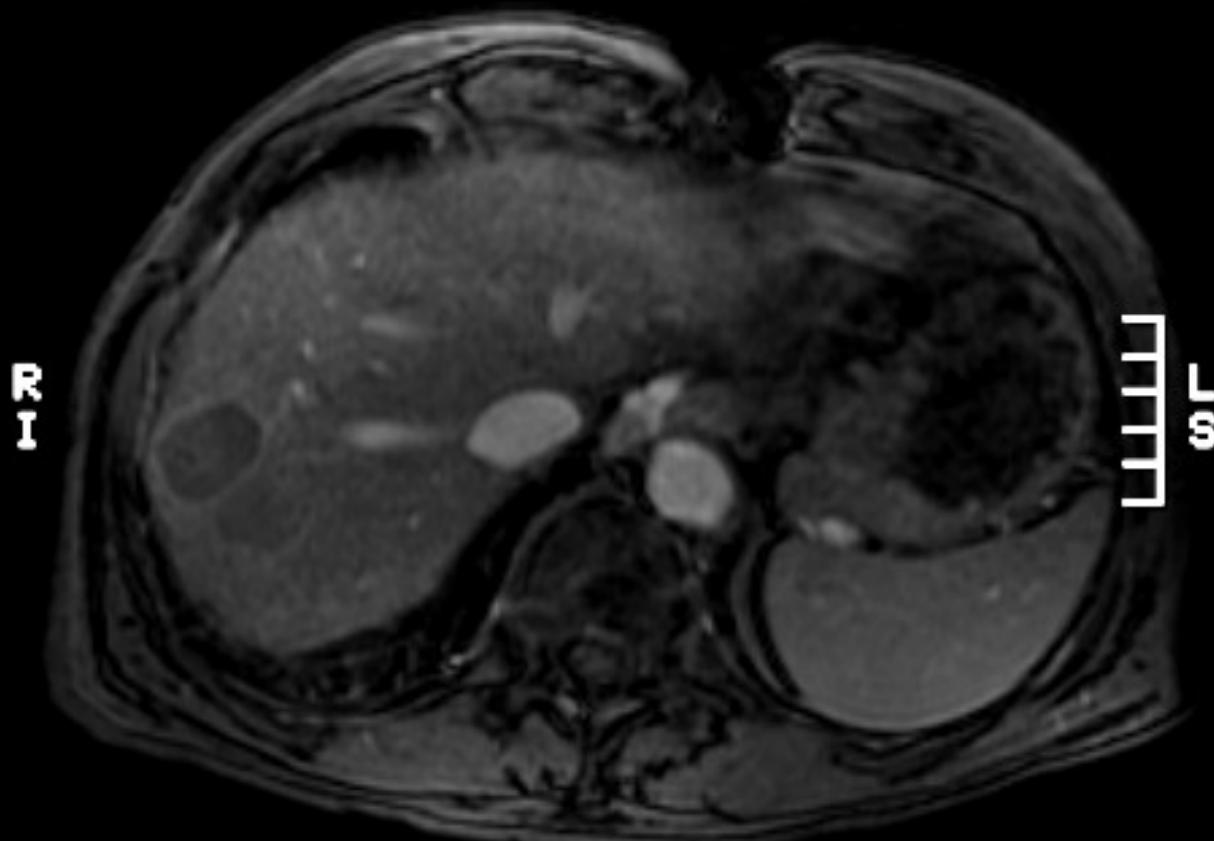


77 yo Caucasian Male with HCV.

AFP 1995-10, 96-12, 98-10, 99-15,
2000 - 598

IM:3

01-Sep-00
4:20:38 PM



P169

W: 750, C: 400
MAG: 179%
2.9:1

Risk Factors for HCV

- ◆ Intravenous Drug Use
- ◆ Blood Product Transfusion
- ◆ Needlestick Injury
- ◆ Sexual Transmission
- ◆ Vertical Transmission
- ◆ Intranasal Cocaine

Hepatitis C Diagnostic Tests

Antibody Tests

- ◆ HCV ELISA
- ◆ HCV IIFA 

Antigen Tests

- ◆ HCV RNA by PCR methodology

HCV Genotype

Treatment - Hepatitis C

1989	HCV antibody discovered
2 May 90	HCV ELISA approved by FDA
1992	Interferon Monotherapy Response SVR 4%-24 wks, 8%-48 wks
1996	Interferon + Ribavirin Response SVR 41%
30 Jan 01	Pegylated Interferon Response SVR 35%
Aug 01	Pegylated Interferon + Ribavirin Response SVR 54%



Hepatitis C Treatment

Pegylated interferon +Ribavirin

Genotype 1 38 - 42%

Genotype 2/3 78 - 82%

- Weight based dosing is recommended for ribavirin and PEG Intron
- 80+80+80 will give higher chance for a sustained response



Interferon

Depression

Neutropenia

Thrombocytopenia

Vascular events

Ribavirin

Anemia

Rash





Extrahepatic Manifestations

- ◆ Cryoglobulinemia
- ◆ PCT
- ◆ Lichen planus
- ◆ Vasculitis
- ◆ Glomerulonephropathy







Hepatitis C Musings N=700 patients

- ◆ 48 % of patients with elevated ALT are not tested for hepatitis C.
- ◆ 20 % of patients with Normal ALT have significant liver disease
- ◆ Many of the patients come with a lot of baggage
- ◆ Treatment with interferon and ribavirin is not easy. Time consuming task.
 - Lots of side effects
 - 50% will require an anti-depressant

Alcohol

- ◆ Increases risk for cirrhosis and liver cancer
- ◆ Shortens the time to develop cirrhosis by as much as 50 %
- ◆ Increases Hep C viral production
- ◆ Reduces response to anti-viral therapy

Heredity Hemochromatosis

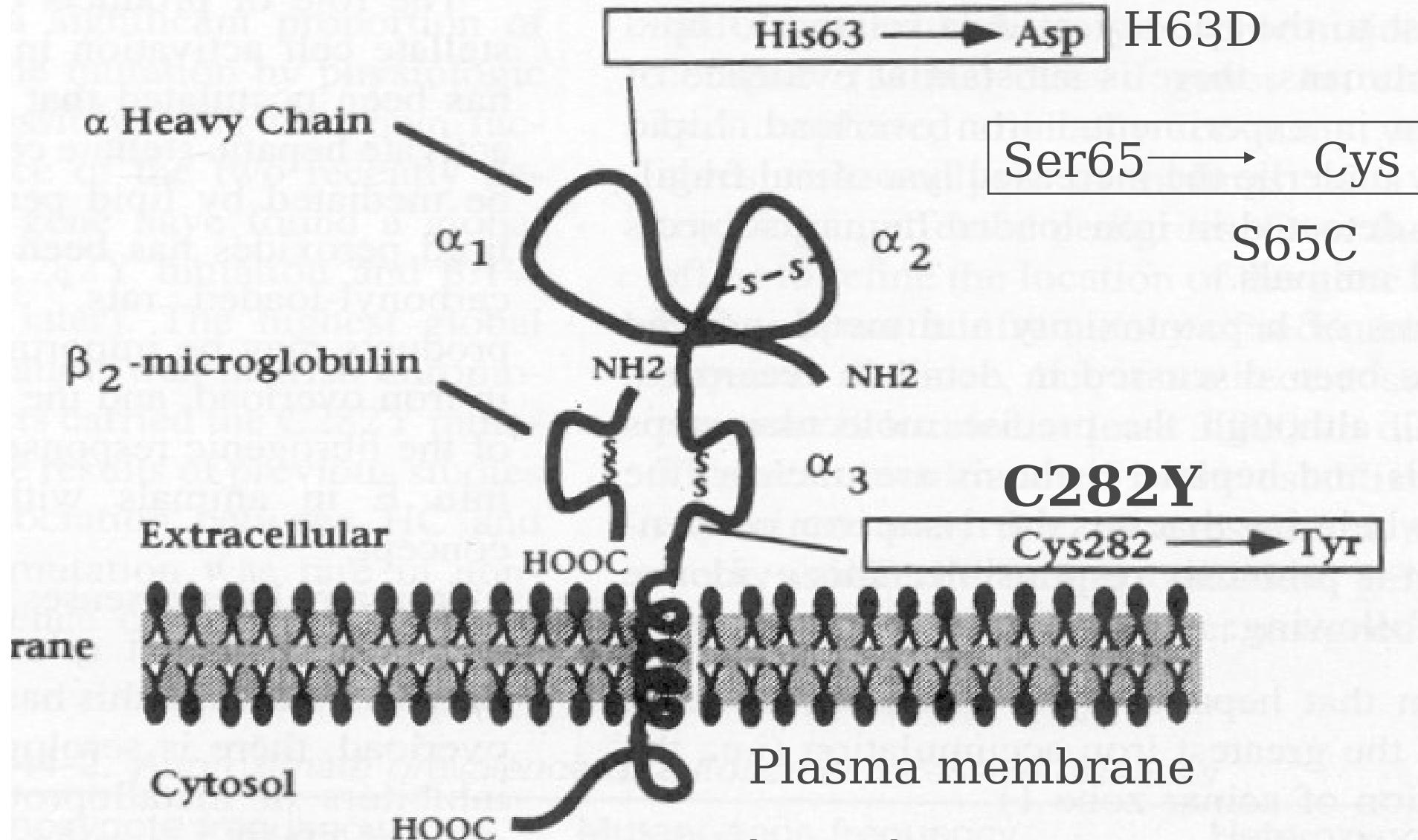
- ◆ Autosomal recessive 1/200 - 1/300
- ◆ Most common genetic disease in persons of European ancestry
- ◆ Associated with diabetes, cardiomyopathy, gonadal failure, arthritis
- ◆ Early detection and treatment can prevent disease complications
- ◆ Treatment: Phlebotomy

Hemochromatosis - Diagnosis

- ◆ Elevated transferrin saturation
 - > 50% in Females
 - > 60% in Males
- ◆ Elevated Ferritin
- ◆ HFE gene determination
- ◆ Liver biopsy if genetic test is negative.

Chromosome 6

Protein product of the HFE gene



Alpha 1-Antitrypsin Deficiency

- Autosomal recessive **1/1600**
- Causes Liver and Pulmonary Disease
- Chromosome 14
- Gene codes for a protease inhibitor

Wilson's Disease

- Autosomal recessive **1/30,000**
- Neurologic and liver disease,
hemolysis
- Chromosome 13

Autoimmune Hepatitis

- ◆ Female:Male 4:1 any age but mostly 20-60 yo
- ◆ Labs
 - + Anti-smooth muscle antibody
 - + Anti-nuclear antibody

Elevated IgG (high total protein with low albumin)
- ◆ High incidence of other autoimmune diseases
- ◆ Progressive disease that leads to cirrhosis unless treated
- ◆ Treatment Steroids and immunosuppressive agents



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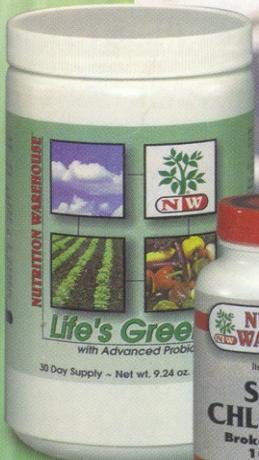
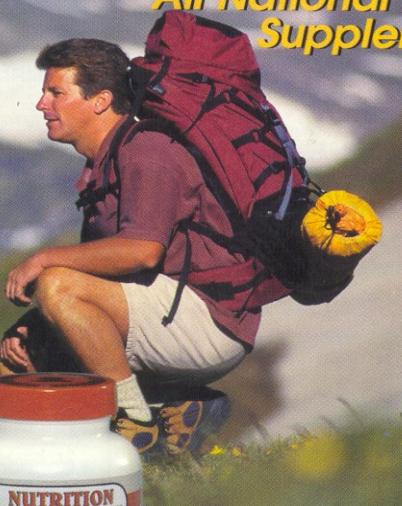
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WARNING:

Page 4:
16 medications you
should NEVER take
with prescription
drugs for sexual
problems.

**Life-Changing News for Men...
And the Women Who Love Them!**

Did this drug cause my patient's hepatitis?

1. Has this type of adverse rxn been observed previously?
2. Was the timing appropriate?
3. Did the problem improve with discontinuation of the drug?
4. Did the problem recur with re-exposure to the suspected culprit?
5. Were other likely causes of hepatitis excluded?

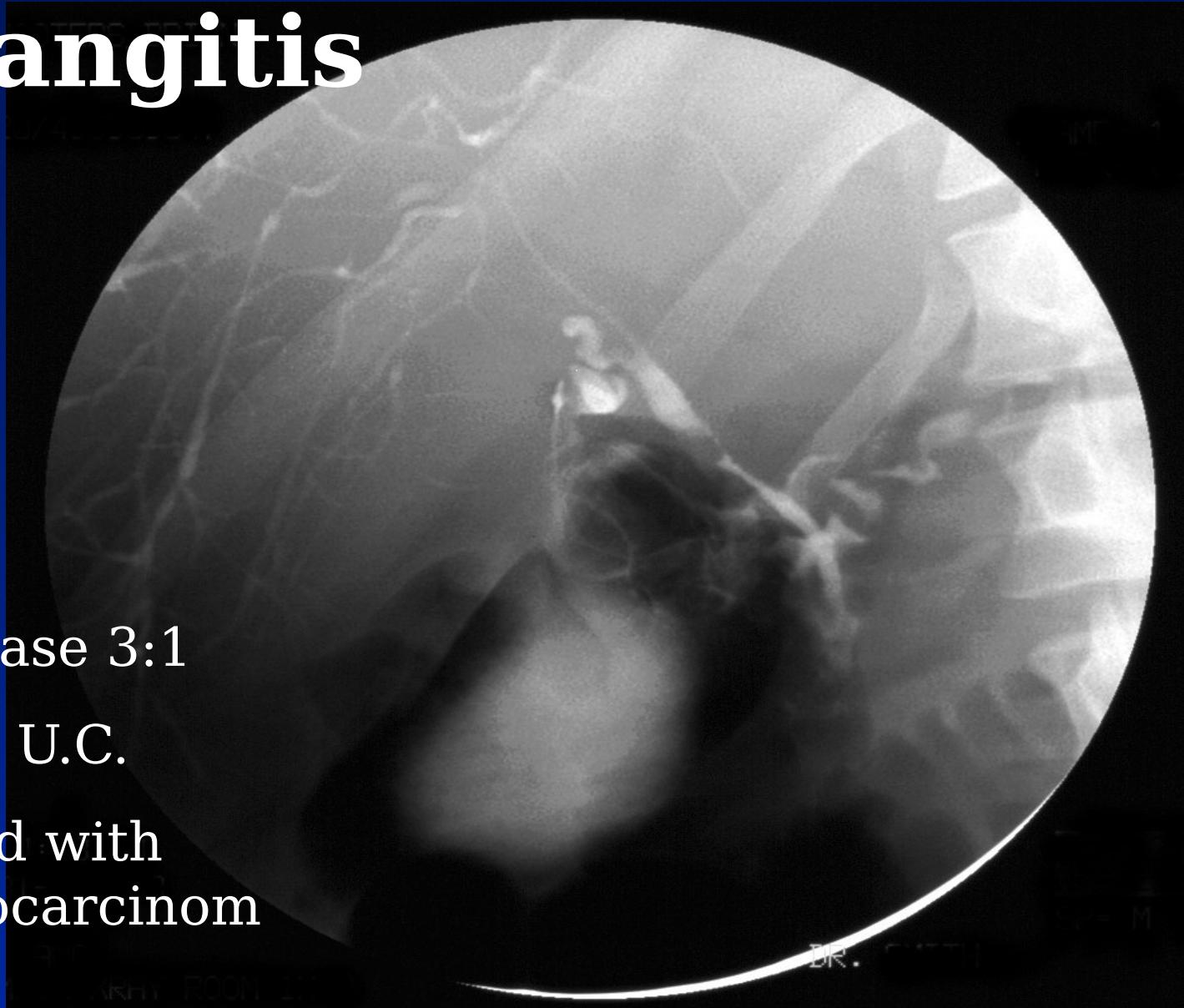
Primary Biliary Cirrhosis

- Women:Male 9:1
- Alk Phos elevated
- Progressive destruction of the small bile ducts
- Positive AMA
- ERCP will be normal



Primary Sclerosing Cholangitis

Male disease 3:1
75% have U.C.
Associated with
Cholangiocarcinom
a



Isolated Mildly Elevated Bilirubin

Primary Differential - Gilbert's Syndrome

- Check record for history of prior elevations
- Fractionate bilirubin (should be all indirect or unconjugated)
- Retic count may be increased
- Increase bilirubin level with stress
- Should be no bilirubin in the urine or any other LAE abnormality

Liver “Enzyme” Patterns

AST/ALT greater than 2
Predictive of ETOH

ALT greater than 5000
Viral
Drugs and Toxins
Ischemia

Summary

- ◆ Upper limit of ALT is set to high
- ◆ R/O Treatable causes of liver disease
- ◆ Fatty liver disease (NAFLD) is a common cause of ALT elevation
- ◆ Therapies are available for HCV and HBV